REMARKS

Claims 6, 13-15, 19-22, 24, 27, 28, 30, 34, and 39 are amended herein. Claims 19, 20, 21, and 39 are amended solely to correct dependency. Support for the amending language of claim 6 is found in the specification on page 6, lines 17-27 and page 15, lines 3-12. Support for the amending language of claims 13-15 is found in the specification on page 7, lines 9-20, page 13, lines 24-29, and on page 15, lines 3-12. Support for the amending language of claims 22 and 24 is found in the specification on page 6, line 28 through page 7, line 1 and on page 8, lines 1-9. Support for the amending language of claims 27 and 28 is found in the specification on page 8, lines 10-15 and on page 14, line 24 through page 15, line 2. Support for the amending language of claim 30 is found in the specification on page 6, line 28 through page 7, line 8. Support for the amending language of claim 34 is found in the specification on page 14, line 24 through page 15, line 2. New claim 42 is added herein. Support for new claim 42 is found throughout the specification, specifically on page 6, lines 17-27, page 12, lines 29-31, and on page 15, lines 3-12.

Claims 4, 5, 9-12, 16-18, 23, 25, 26, 29, 32, 33, 37, 38, 40, and 41 are cancelled herein, without prejudice to renewal. After entry of this amendment, claims 1-3, 6-8, 13-15, 19-22, 24, 27, 28, 30, 31, 34-36, 39, and 42 are pending in the application.

No new matter is added. Reconsideration of the subject application is respectfully requested.

Priority

Applicants note that the instant application is a national phase application under § 371. Consequently, it is not necessary for the Applicants to amend the first sentence of the specification to reference the international application number (see § 1893.03(c) of the MPEP, Original 8th Edition, August 2001, with Revision 1, February 2003). No claim for priority under 35 U.S.C. § 120 is asserted in the present application.

Claim Rejections – 35 U.S.C. § 101

Claim 26 was rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter for reading on a product of nature. Claim 26 is cancelled herein, thereby rendering this rejection moot.

Claim Objections

Claims 8 and 9 were objected to for being identical. Claim 9 is cancelled herein, thereby rendering this objection moot.

Claim 40 was objected to for a typographical error. Claim 40 is cancelled herein, thereby rendering this objection moot.

Claim Rejections – 35 U.S.C. § 112

Claims 13-17, 32, 33, and 41 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Office action asserts that claims 13-17 are indefinite for including a combination of conditional claim limitations and setting forth claim limitations in the future tense. Furthermore, claims 13-17 were rejected for allegedly not comprising a specific amount of conjugate.

Claims 16 and 17 are cancelled herein, thereby rendering this rejection moot as applied to these claims. Claims 13-15 are amended herein to depend from claim 6, to remove conditional claim limitations, to recite a "therapeutically effective" amount of conjugate, and to be in the present tense. Applicants submit that these amendments remove the rejection of claims 13-15.

Claim 32 was rejected as allegedly being indefinite. Claim 32 is cancelled herein, thereby rendering this rejection moot.

Claim 33 was rejected as allegedly being indefinite. Claim 33 is cancelled herein, thereby rendering this rejection moot.

Claim 41 was rejected as allegedly being incomplete. Claim 41 is cancelled herein, thereby rendering this rejection moot.

Claim Rejections – 35 U.S.C. § 102

Claims 1-3, 6, 8, 9, 10-17, 19-26, 30-34, and 40 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Konadu *et al.*, *J. Infect. Diseases* 177:383-87, February 1998

(Konadu *et al.* 1998). The Office action asserts that Konadu *et al.* 1998 constitutes a different inventive entity. Applicants respectfully disagree with this rejection.

As shown in the Declaration of Drs. Shousun Chen Szu and John B. Robbins, Konadu *et al.* 1998 is in fact the work of the Applicants, published less than one year before the filing date of the present application. Thus, Konadu *et al.* 1998 is not available as prior art. This Declaration is submitted unsigned as Dr. Robbins is not currently available. A signed copy of the Declaration will be submitted to the U.S. PTO immediately upon receipt. In light of the Declaration, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 10-17, 22, 24, and 26 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Konadu *et al.*, *Infection and Immunity* 62:5048-54, 1994 (Konadu *et al.* 1994). Claims 10-12, 16, 17, and 26 are cancelled herein, thereby rendering this rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to pending claims 13-15, 22, and 24.

Konadu *et al.* 1994 discloses *E. coli* O157 O-specific polysaccharide-protein conjugate vaccines wherein the O-specific polysaccharide is conjugated to bovine serum albumin (BSA), exotoxin C of *Clostridium welchii* and *Pseudomonas aeruginosa* exoprotein A. These O-specific polysaccharide-protein conjugate vaccines elicited antibodies with bactericidal activity to the O157 O-specific polysaccharide in mice.

Konadu *et al.* 1994 does not disclose, nor render obvious, the use of Shiga toxin as a carrier protein, nor the production of antibodies to Shiga toxin. Amended claims 13-15, 22, and 24 are directed to compositions comprising *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates and isolated human antibodies which are immunoreactive with such conjugates. Therefore, Konadu *et al.* 1994 does not anticipate amended claims 13-15, 22, and 24. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-6, 8-11, 13-17, 19-22, 24-26, 34-39, and 40 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Konadu *et al.*, symposium presentation, 1997 (Konadu *et al.* 1997). The Office action states that Konadu *et al.* 1997 discloses an *E. coli* O157 O-specific polysaccharide/Shiga toxin conjugate (referencing "all slides"), and asserts that Konadu *et al.* 1997, therefore, inherently anticipates claims 1-6, 8-11, 13-17, 19-22, 24-26, 34-39, and 40.

Applicants respectfully disagree with this rejection. Section 2128.01 ("Level of Public Accessibility Required") of the MPEP notes that "A paper which is orally presented in a forum open to all interested persons constitutes a 'printed publication' if written copies are disseminated without restriction. *Massachusetts Institute of Technology v. AB Fortia*, 774 F.2d 1104, 1109, 227 USPQ 428, 432 (Fed. Cir. 1985)."

In a case more exactly on point, the U.S. District Court for the District of New Jersey held that slides projected on a screen during an oral presentation did not constitute a "printed publication" under the theory that transient projection of slides does not disclose an invention to the extent necessary to enable a person of ordinary skill in the art to make or use the invention. *Regents of the Univ. of Calif. v. Howmedica, Inc.*, 530 F. Supp. 846, 860 (D.N.J. 1981), aff'd, 676 F.2d 687 (3rd Cir. 1982). The Court went on to state:

> In this regard, it is important to note that the public did not have access to the slides prior to the critical date, and that no prints of the slides were made prior to said date. Therefore, there is no evidence that the "publication" was disseminated or otherwise made available to the extent that persons interested in the information could locate it and put to use the essentials of the claimed invention [citation omitted]. *Id* at 860.

As shown in the Declaration of Dr. Shousun Chen Szu, submitted herewith, Dr. Szu made the symposium presentation using the referenced slides, the public did not have access to the slides prior to the presentation, and no prints of the slides were disseminated to the public.

In light of the foregoing arguments and the Declaration submitted herewith, Applicants submit that claims 1-6, 8-11, 13-17, 19-22, 24-26, 34-39, and 40 cannot be inherently anticipated by the Konadu *et al.* 1997 oral presentation. Reconsideration and withdrawal of the rejection is respectfully requested. In the unlikely event that this rejection is maintained, Applicants respectfully request that the slide or slides that inherently anticipate claims 1-6, 8-11, 13-17, 19-22, 24-26, 34-39, and 40 be specified.

Claims 10 and 13-18 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Moreau *et al.*, U.S. Patent No. 6,472,506 (the '506 patent). The Office action states that the '506 patent has an effective filing date of January 21, 1997.

Applicants respectfully disagree with this rejection. Applicants submit that the effective filing date of the '506 patent is November 4, 1998, which is after the priority date of the present application, July 20, 1998. Applicants submit herewith a copy of the "Flowcharts for 35 U.S.C. § 102(e) Dates" as found in § 706.02(f)(1) of the MPEP, as Exhibit A. The portion highlighted shows that the § 102(e) date for a U.S. patent based on an International Application (IA) filed before November 29, 2000 is the § 371(c)(1), (2) and (4) date. The '506 patent is based on an IA filed January 21, 1998 and the § 371(c)(1), (2) and (4) date is November 4, 1998. Thus, the '506 patent is not prior art. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 22 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chart *et al.*, *J. Clinical Micro.* 27:285-90, 1989. Applicants respectfully disagree with this assertion as applied to amended claim 22.

Chart *et al.* discloses sera from subjects with hemolytic uremic syndrome that contains antibodies against *E. coli* O157 O-specific polysaccharide. Chart *et al.* does not disclose, nor render obvious, compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide conjugated to a Shiga toxin carrier protein. Amended claim 22 is directed to a composition comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates. Therefore, Chart *et al.* does not anticipate amended claim 22. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 22 was also rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Vernozy-Rozand, C., *J. Applied Micro.* 82:537-51, 1997. Applicants respectfully disagree with this assertion as applied to amended claim 22.

Vernozy-Rozand, C. discloses antisera against the O and H antigens of *E. coli* O157. Vernozy-Rozand, C. does not suggest, nor render obvious, compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide conjugated to a Shiga toxin carrier protein. As discussed above, amended claim 22 is directed to a composition comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates. Therefore, Vernozy-Rozand, C. does not

anticipate amended claim 22. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 22-26 and 40 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Johnson *et al.*, *Infection and Immunity* 64:1879-83, 1996. Claims 23, 25, 26, and 40 are cancelled herein, thereby rendering this rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to pending claims 22 and 24.

Johnson *et al.* discloses **bovine** antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide and verotoxin 1 (also known as Shiga toxin 1). Johnson *et al.* does not suggest, nor render obvious, compositions comprising isolated **human** antibodies (such as from plasma, serum, or immunoglobulin) immunoreactive with *E. coli* O157 O-specific polysaccharide conjugated to a Shiga toxin carrier protein. Amended claims 22 and 24 are directed to compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates, including human plasma, serum, and immunoglobulin. Therefore, Johnson *et al.* does not anticipate amended claims 22 and 24. Reconsideration and withdrawal of the rejection is respectfully requested. Additionally,

Claim 40 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ashkenazi *et al.*, *J. Peds.* 113:1008-14, 1988; Bitzan *et al.*, *Infection* 21:140-45, 1993, and under 35 U.S.C. § 102(e) as allegedly being anticipated by Burnie *et al.*, U.S. Patent No. 6,410,024. Claim 40 is cancelled herein, thereby rendering these rejections moot.

Claims 22, 24, and 26-28 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chidlow *et al.*, U.S. Patent No. 4,141,970 (the '970 patent). Claim 26 is cancelled herein, thereby rendering this rejection moot as applied to this claim. Applicants respectfully disagree with this assertion as applied to pending claims 22, 24, 27, and 28.

The '970 patent teaches a method of actively immunizing a pregnant mammal with effective amounts of *E. coli* O157 endotoxin, such that her young are passively immunized (via colostrum) against *E. coli* O157.

The '970 patent does not suggest, nor render obvious, compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B

subunit conjugates, including human plasma, serum, and immunoglobulin, and their uses in the passive immunization of a human. As discussed above, amended claims 22 and 24 are directed to compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates, including human plasma, serum, and immunoglobulin. Amended claims 27 and 28 teach methods of passively immunizing a human against *E. coli* O157, comprising administering an immunologically sufficient amount of a composition comprising human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates. Therefore, the '970 patent does not anticipate amended claims 22, 24, 27, and 28. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 40 and 41 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Harari *et al.*, *Infection and Immunity* 56:1618-24, 1988. Claims 40 and 41 are cancelled herein, thereby rendering this rejection moot.

Claim Rejections – 35 U.S.C. § 103

Claim 34 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Robbins *et al.*, *Reviews of Infect. Dis.* 13:S362-5, 1991. Applicants respectfully disagree with this assertion as applied to amended claim 34.

Robbins *et al.* teaches experimental vaccine conjugates for the prevention of Shigellosis, comprising the O-specific polysaccharide side chains of *Shigella dysenteriae* type 1, *Shigella flexneri* type 2A and *Shigella sonnei* smooth phase conjugated to tetanus toxoid carrier protein. Robbins *et al.* suggests the possibility of using the B subunit of Shiga toxin as a carrier protein in preparing vaccine conjugates for the prevention of Shigellosis. There is no suggestion or motivation in Robbins *et al.* to modify their teachings and prepare conjugate molecules comprising an *E. coli* O-specific polysaccharide and a carrier protein such as tetanus toxoid, let alone conjugate molecules comprising an *E. coli* O-specific polysaccharide and the B subunit of Shiga toxin. Consequently, Applicants submit that Robbins *et al.* does not render obvious claim 34. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 10-18, 20-22, 24, 26-29, 32, and 33 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Konadu *et al.* 1994 in view of Lees, A., U.S. Patent No. 5,693,326 (the '326 patent). Claims 10-12, 16-18, 26, 29, 32, and 33 are cancelled herein, thereby rendering this rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to pending claims 13-15, 20-22, 24, 27, and 28.

As previously discussed, Konadu *et al.* 1994 discloses *E. coli* O157 O-specific polysaccharide-protein conjugate vaccines wherein the O-specific polysaccharide is conjugated to BSA, exotoxin C of *Clostridium welchii* and *Pseudomonas aeruginosa* exoprotein A. These O-specific polysaccharide-protein conjugate vaccines elicited antibodies with bactericidal activity to the O157 O-specific polysaccharide in mice. The '326 patent discloses conjugates comprising carbohydrate-containing moieties selected from *E. coli* and protein moieties such as BSA, tetanus toxoid, pertussis toxoid, and diphtheria toxoid.

Amended claims 22 and 24 are directed to compositions comprising isolated human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates, including human plasma, serum, and immunoglobulin. Amended claims 27 and 28 teach methods of passively immunizing a human against *E. coli* O157, comprising administering an immunologically sufficient amount of a composition comprising human antibodies immunoreactive with *E. coli* O157 O-specific polysaccharide/Shiga toxin B subunit conjugates.

The Office action states that it would have been obvious to a person of ordinary skill in the art to combine the *E. coli* O157 O-specific polysaccharide disclosed by Konadu *et al.* 1994 with the carrier proteins (tetanus toxoid, pertussis toxoid and diphtheria toxoid) as disclosed by the '326 patent.

The legal standard applicable to determinations of obviousness based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art [citations omitted]. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** [emphasis added].

Therefore, three elements must be established in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide the incentive for, the combination of references. Second, the combination as suggested or motivated by the art must yield the process or invention claimed. Third, the prior art must provide a reasonable expectation of success of the claimed process. At no point may the applicant's disclosure be used to satisfy the three elements. If any of these elements is absent, the rejection based on obviousness is unsupported.

In the present case, Applicant submits that no case of obviousness has been established. Nothing in Konadu *et al.* 1994, which discloses *E. coli* O157 O-specific polysaccharide, suggests or provides a motivation for combination with the '326 patent, which discloses tetanus toxoid, pertussis toxoid and diphtheria toxoid carrier proteins, let alone conjugate molecules comprising an *E. coli* O-specific polysaccharide and the B subunit of Shiga toxin. Nor is there any suggestion or motivation that such an impermissible modification would have a reasonable expectation of success. Consequently, Applicants submit that the combination of Konadu *et al.* 1994 and the '326 patent do not suggest, nor render obvious, the subject matter of pending claims 13-15, 20-22, 24, 27, and 28. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 4, 5, 7, 37, and 38 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Konadu *et al.* 1998 in view of the '326 patent. Claims 4, 5, 37, and 38 are cancelled herein, thereby rendering this rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to pending claim 7, which discloses pharmaceutical compositions of *E. coli* O-specific polysaccharide/Shiga toxin B subunit conjugates.

As discussed above, Konadu *et al.* 1998 is not available as prior art. The '326 patent discloses conjugates comprising carbohydrate-containing moieties selected from *E. coli* and protein moieties such as BSA, tetanus toxoid, pertussis toxoid, and diphtheria toxoid. It does not disclose pharmaceutical compositions of *E. coli* O-specific polysaccharide/Shiga toxin B subunit conjugates. Therefore, the '326 patent does not suggest, nor render obvious, the subject matter of pending claim 7. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 34-36 and 39 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Konadu *et al.* 1998 in view of Taylor *et al.*, *Infection and Immunity* 61:3678-87, 1993. Applicants respectfully disagree with this assertion as applied to claims 34-36 and 39, which disclose conjugate molecules comprising an *E. coli* O-specific polysaccharide and the B subunit of Shiga toxin.

As previously discussed, Konadu *et al.* 1998 is not available as prior art. Taylor *et al.* discloses conjugate vaccines composed of the O-specific polysaccharide side chains of *Shigella dysenteriae* type 1, *Shigella flexneri* type 2A and *Shigella sonnei* smooth phase bound to carrier proteins including tetanus toxoid and recombinant *Pseudomonas aeruginosa* exoprotein A. It does not disclose conjugate molecules comprising an *E. coli* O-specific polysaccharide and the B subunit of Shiga toxin. Therefore, Taylor *et al.* does not suggest, nor render obvious, the subject matter of claims 34-36 and 39. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office action cites the following additional references as being duplicative of the above applied alleged prior art: Aanon *et al.*, U.S. Patent No. 5,204,097; Bundle *et al.*, U.S. Patent No. 6,310,043; Chae *et al.*, U.S. Patent No. 6,162,441; Cryz *et al.*, U.S. Patent No. 5,370,872; Doyle *et al.*, U.S. Patent No. 5,354,661; Keusch *et al.*, U.S. Patent No. 5,955,293; Krivan *et al.*, U.S. Patent No. 5,512,282; O'Brien *et al.*, U.S. Patent No. 5,747,272; Porro *et al.*, U.S. Patent No. 5,153,312; Samuel *et al.*, U.S. Patent No. 5,552,144; Dick *et al.*, *Contrib. Mol. Immunol.* 10:48-114, 1989; Chu *et al.*, *Infect. and Immunity*, 1991; Gupta *et al.*, *Infect. and Immunity*, 1995; Islam *et al.*, *J. Clin. Lab. Immunol.*, 1990; Havens *et al.*, *Microb. Immunol.*, 1992; Padhye *et al.*, *J. Clin. Micro.*, 1991; Ryd, Marie, *Ph.D. thesis*, Karolinska Institute, Sweden, 55:02-C, p.432, 1992; Qadri *et al.*, *Adv. Mucosal Immunol.*, 1995; Schmitt *et al.*, *Infect. and Immunity*, 1991; and Weinstein *et al.*, *Infect. and Immunity*, 1989.

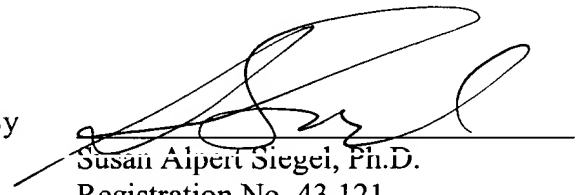
Absent rejections based on specific references, Applicants are unable to substantively address these references. Therefore, Applicants submit that it would be improper to issue a final Office action.

Conclusion

Based on the foregoing, Applicants believe that pending claims 1-3, 6-8, 13-15, 19-22, 24, 27, 28, 30, 31, 34-36, 39, and 42 are in condition for allowance. If any matters remain to be addressed before a Notice of Allowance is issued, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 
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